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Clinical Usefulness of Apomorphine in Movement Disorders

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Summary: Apomorphine, the first dopamine agonist to be synthesized, has received a renewed interest in the last few years. This compound acts powerfully on D_1 and D_2 dopamine receptors and has the most complete pharmacological profile of all clinically available dopamine agonists. When given subcutaneously, apomorphine consistently reverses levodopa-resistant "off" periods in parkinsonian subjects: thus, it is used in cases with severe motor fluctuations, either by continuous infusion with a portable pump or by multiple injections. Studies based on this approach have been highly encouraging, as they have shown a significant reduction in off time and a good drug tolerability. The main side effect has been the occurrence of nodular skin lesions, especially when continuous infusions were used. At variance with other dopamine agonists, a low incidence of psychiatric morbidity has been reported with apomorphine. The few available comparative reports have shown that this compound is more potent and better tolerated than lisuride. Parenteral apomorphine has been used in Parkinson's disease (PD) to replace levodopa after surgery or to treat the malignant syndrome brought about by sudden levodopa withdrawal. Acute challenge with apomorphine has been used to test dopaminergic responsiveness in parkinsonian syndromes and in dystonia. The clinical response to apomorphine may predict the effect of a chronic therapy with levodopa in ~90% of PD cases. Further studies are still necessary to evaluate the exact relationship between the acute response to apomorphine and a chronic therapy. In addition, apomorphine has been used to conduct clinical pharmacological studies in PD, for it is particularly well suited for research on the pharmacodynamics of central dopamine receptors. In summary, apomorphine appears to be an efficacious and safe drug for the treatment of advanced PD. It must still be considered under clinical evaluation as a test drug for acute challenge in PD and dystonia. Finally, in our opinion, the available data suggest apomorphine (in conjunction with domperidone) as a first-choice treatment for the neuroleptic malignant syndrome and the temporary replacement of levodopa (e.g., after gastrointestinal surgery). **Key Words:** Apomorphine—Dopamine—Dystonia—Huntington's disease—Levodopa—Lisuride—Parkinson's disease.

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Apomorphine was first synthesized in 1869, when Matthiessen and Wright noted that, when morphine was dehydrated with hydrochloric acid, a skeletal rearrangement led to the formation of a new molecule (1); they called this compound apomorphine (10,11-dihydroxyaporphine). Although derived from morphine, apomorphine has little pharmacological similarity with this narcotic analgesic. Its emetic properties were described in 1869 by Gee, who also reported the case of a boy whose maniacal state improved after apomorphine administration (2). Toward the end of the 19th century, the sedative–hypnotic properties of apomorphine were reported by several other authors, who administered lower doses than those necessary to induce emesis (3). These observations supported the use of apomorphine in the treatment of several psychiatric disorders, including schizophrenia, manic states, idiopathic depression, delirium tremens, neurosis with panic attacks, and sleeplessness. In 1884, Weil treated various motor disturbances with apomorphine, including chorea, jacksonian epilepsy, and hiccoughs (4). The efficacy of this approach led him to first propose the use of apomorphine in Parkinson's disease (PD).

PHARMACOLOGY

The precise chemical structure of apomorphine was elucidated in 1902 (5), but only recently it was shown that it remarkably recalls the structure of dopamine (6). In these early reports, two main clinical features of apomorphine were repeatedly documented: a short duration of action and the occurrence of side effects, such as nausea, vomiting, sedation, yawning, bradycardia, and postural hypotension. The various actions of apomorphine, on both experimental animals and humans, were known long before they were recognized as due to a stimulation of central and peripheral dopamine receptors. Among all the available synthetic dopamine agonists, apomorphine is the one with a pharmacological profile most closely related to that of dopamine. Indeed, apomorphine has a rather high affinity for dopamine receptors; its reactivity constant (K_i) values indicate a fairly good affinity for D_2, D_3, and D_4 receptors and much less affinity for D_1 and D_5 receptors. This means that apomorphine has an approximately 10-fold higher affinity for D_2 than for D_1 dopamine receptors (7). In this respect, apomorphine differs from all ergot derivatives, which are mainly or uniquely D_2 receptor agonists.

The peripheral pharmacokinetic of parenteral apomorphine was elucidated in humans quite recently. Evaluations based on a two-compartment model have reported that the distribution half-life is 4.8 ± 1.1 min, and that the elimination half-life is 33.6 ± 3.9 min (8). After a single subcutaneous injection, apomorphine is rapidly absorbed, with peak plasma concentrations occurring as early as 3 min after the administration. After an injection in parkinsonian subjects, the clinical effect on movement usually begins within 6–8 min and lasts for 40–90 min. The drug equilibrates quickly between blood and tissue compartments, including brain, because of its high solubility in lipids. As a consequence of lipophilia, brain concentrations are up to eight times higher than those occurring in plasma. The elimination half-life, calculated for subcutaneous administration, is similar to that for the intravenous route. This suggests that apomorphine is completely absorbed

from the subcutaneous tissue (more rapidly after an injection in the anterior abdominal wall); thus, in clinical practice, subcutaneous infusions appear to be as efficacious as intravenous ones. The activity after oral administration is, on the contrary, quite low: this is due to poor bioavailability of the drug, mainly related to a strong "first-pass" hepatic metabolism (9).

Peripheral side effects of apomorphine have hindered its diffusion as a therapeutic agent. It was only after the discovery that domperidone is a D_2 dopamine receptor blocker that does not cross the blood–brain barrier (10) that apomorphine could be used, in association with this antidote, as an effective therapeutic agent (11). Pretreatment with domperidone not only increases tolerability but can also prevent cardiovascular reflex changes induced by apomorphine (12). Based on these premises, apomorphine has been increasingly used in neurological practice in conjunction with domperidone. Furthermore, after the introduction of new drug-delivery systems, the short half-life of apomorphine does not constitute a major limitation to its clinical use.

PARKINSON'S DISEASE

Therapeutic Use

Early Investigations

Based on the experimental evidence that apomorphine abolished decerebrated rigidity in animals, Schwab and co-workers proposed in 1951 to use it as an antiparkinsonian agent, particularly to treat rigidity and tremor (13). This observation did not result in a new approach in clinical practice, due to the variety of side effects already mentioned. The antiparkinsonian activity of apomorphine was later reconsidered, based on the discovery that it is a potent dopamine receptor agonist (14). Its use as antiparkinsonian agent was proposed again in 1970 (15). Apomorphine was administered subcutaneously (0.25–2 mg in each injection) to untreated patients or to patients who had already benefited from levodopa. In this study, similarities between the antiparkinsonian properties of levodopa and those of apomorphine were observed (15). The same authors later reported also on the efficacy of the oral administration of apomorphine (150–1440 mg/day); they observed that, when doses were slowly increased, apomorphine did not produce a great number of side effects, most patients being able to tolerate the medication. Unfortunately, at the high doses employed, a dose-dependent, reversible elevation of serum urea and creatinine, with no other changes in electrolytes or urinalysis, was observed (16). In summary, although the efficacy of apomorphine in PD was confirmed, the severity of the observed side effects (compared to those of levodopa) and the short duration of each parenteral administration significantly limited the therapeutic profile.

Current Indications

PD is characterized by an initial favorable and stable motor response to levodopa, which subsequently results in the appearance of disabling fluctuations in motor performance. Although it is not difficult to treat the disease at early stages,

the availability of a wide array of drugs is necessary for fluctuating patients. Many mechanisms have been proposed to explain levodopa-related motor fluctuations, including levodopa peripheral pharmacokinetics, erratic absorption at gastric level, increased production of 3-*O*-methyl-3,4-dihydroxyphenylalanine (DOPA), loss of storage at the presynaptic dopaminergic terminals, and pharmacodynamic postsynaptic receptor modifications (17). It has become increasingly evident that severe motor fluctuations, such as those observed in most parkinsonian patients after several years of disease duration, cannot be easily overcome by a simple adjustment of the levodopa daily schedule or by the addition of available dopamine agonists given orally.

Continuous dopaminergic stimulation (via parenteral administration) has been proposed as a method for stabilizing motor conditions in patients with frequent fluctuations and severe off periods. Several different drugs and delivery systems have been suggested. Unfortunately, levodopa is poorly water soluble and is not easily amenable to parenteral administration (18). Although levodopa can be conjugated to acquire water solubility, its carrier system through the blood–brain barrier is influenced by the oral intake of large neutral amino acids. The most commonly known soluble conjugate of levodopa is the methyl ester, which brings a potential toxicity from its breakdown product, methanol (19).

Based on this, it was thought that, to overcome motor fluctuations, the continuous parenteral infusion of a potent dopamine agonist for most of the day could be substituted for or, more often, be added to oral levodopa. Indeed, the clinical efficacy of dopamine agonists would be independent of any competition with dietary amino acids at the blood–brain barrier. Due to their high solubility in water, apomorphine and lisuride are the natural candidates for subcutaneous administration. A first clinical trial with lisuride showed a marked improvement in those severely fluctuating patients who were able to tolerate the drug (20). A direct comparison of apomorphine to lisuride in two patients showed that apomorphine is more potent and better tolerated than lisuride (21). Additional reports directly comparing apomorphine and lisuride are remarkably lacking (22). We observed a patient in whom lisuride and apomorphine were infused on consecutive days at increasing doses: the tolerability/efficacy ratio showed a marked difference in favor of apomorphine, which was the only drug able to switch the patient on without the association of levodopa. Long-term results of lisuride have confirmed that its parenteral use is complicated by a significantly high incidence of severe psychiatric side effects (in 44% of cases), possibly due to its serotoninergic properties (23). The experience with apomorphine infusions is reported subsequently.

Subcutaneous Administration

After the demonstration that single injections of apomorphine reliably and effectively improve motor performance during levodopa-resistant off periods (24), Stibe and co-workers reported the preliminary results of apomorphine infusion in six parkinsonian patients with on–off fluctuations and levodopa-resistant off periods (21). Apomorphine was continuously administered by means of a portable

battery pump, usually incorporating a booster function to give a bolus on demand. A butterfly needle was inserted subcutaneously in the abdomen and changed once daily. This study indicated a marked reduction in the number of hours spent in the off period per day, without significant side effects. The oral administration of domperidone almost abolished nausea, vomiting, and postural hypotension.

Two larger reports from the same group later confirmed the efficacy of continuous daytime (or, in some cases, around-the-clock) apomorphine in a larger group of patients (25,26). Levodopa requirements were significantly reduced after apomorphine, and a few selected patients discontinued levodopa completely. In a separate group with shorter and less frequent off periods, single injections of apomorphine were intermittently administered by a manual pen-like device for self-injections commonly used to deliver insulin. Such a device could conveniently release repeated single subcutaneous doses of preset amounts of the solution. The injections were delivered into the abdomen or the thighs by the same patients, who were advised to anticipate the off periods. When this was not possible, the patients needed to be injected by their spouses or caregivers.

Hughes and colleagues reported on a long-term follow-up of these patients (27). Intermittent or continuous apomorphine was administered to 108 patients, for up to 5 years. Apomorphine reduced the daily off periods by an average 50%. These excellent results were maintained throughout the following years, with a low incidence of psychiatric morbidity (overall 21%, mainly mild symptoms). Apomorphine appeared not to produce appreciable tolerance or loss of therapeutic efficacy with time. Moreover, in some cases, it was possible to progressively reduce and eventually withdraw domperidone. Similar findings were reported by other European groups (28–37), whose results are summarized in Tables 1 and 2. Based on such a wide experience, it appeared that the long-term therapeutic response to apomorphine was frequently marred by the occurrence of severe on dyskinesias, even though in a few cases, apomorphine infusion led to a progressive reduction of the severity of dyskinesias. The latter observation is of special interest, as it might reflect the occurrence of striatal dopamine receptor desensitization after a continuous stimulation by apomorphine.

The most frequent side effect observed in patients using apomorphine infusions has been local skin reactions, followed by the development of itchy fibrotic nodules at the needle-insertion points. These may scab and break down and occasionally become infected or bleed. It is nevertheless possible to minimize these local reactions by adding saline to the solution to dilute apomorphine from the usual 10 mg/ml to 5 mg/ml or less and by frequently changing the injection sites (38). A drug-dependent, reversible Coombs-positive hemolytic anemia has been described in few cases treated with apomorphine and levodopa; a specific pathogenetic role of apomorphine has not been documented in these cases, because autoimmune hemolytic anemia is a well-known side effect of α-methyldopa treatment and has already been described in patients treated with levodopa alone (26,35).

The patients who can expect to have a significant therapeutic benefit from apomorphine are those with severe off periods and with a good quality of on periods (particularly if not associated with troublesome peak or interdose dyski-

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TABLE 1. *Summary of the main findings of studies reporting on intermittent injections of apomorphine in PD*[a]

Clinical feature	Ref. 29	Ref. 26	Ref. 31	Ref. 33	Ref. 34	Ref. 36	Ref. 37	Synopsis
Number of patients studied	7	32	5	6	19	7	6	82
Mean dose of apomorphine in each injection (mg)	4.7	2.2	2.1	2.8	2.6	4.1	2.5	3
Mean number of injections per day		4.8	4.2	3.8		3.3	3.3	3.9
Mean reduction in *off* time	63.3%	58%	63%	8.5%		55%	32.6%	46.7%
Mean reduction in levodopa	0%	4.6%	14%			0%	0%	3.7%
Side effects (incidence)								
Skin nodules or local skin reaction		Yes	20%		100%	Yes	0%	40%
Psychiatric signs			0%		26.3%		0%	8.8%
Orthostatic hypotension		6.3%	0%	16.7%	5.3%		33.3%	12.3%
Priapism					5.3%		16.7%	11%
Eosinophilia	Yes		20%			10.5%	0%	10.2%
Hyperlibido		3.1%					0%	1.5%

[a] A synopsis of the data on the clinical efficacy and the occurrence of side effects is reported in the rightmost column. The mean incidence of side effects is based only on data clearly reported in the literature.

TABLE 2. *Summary of the main findings of studies reporting on continuous infusion of apomorphine in PD*[a]

Clinical feature	Ref. 30	Ref. 26	Ref. 31	Ref. 34	Ref. 35	Ref. 37	Synopsis
Number of patients studied	7	25	9	3	18	10	72
Mean dose of apomorphine (mg/h)	3	3.3	5.4	7	7	2.6	4.7
Mean duration of infusion (h)	10	20.1	18.7	12	24	10.1	15.8
Mean reduction in *off* time	85%	54.5%	67%	67.7%	57.9%	32%	60.6%
Mean reduction in levodopa	39%	21.9%	53%	52%	20%	12.7%	33.1%
Side effects (incidence)							
Skin nodules or local skin reaction	28.6%	100%	100%	100%	27.8%	10%	61.1%
Eosinophilia		10%	44.4%	33.3%	16.7%	0%	20.9%
Orthostatic hypotension	28.6%		0%		0%	10%	9.6%
Psychiatric signs	14.3%	16%			16.7%	0%	11.7%
Hemolitic anemia		4%	0%		11.1%	0%	3.8%
Excessive sedation					16.7%	10%	13.3%
Increase of on dyskinesia		16%			0%	20%	12%

[a] A synopsis of the data on the clinical efficacy and the occurrence of side effects is reported in the rightmost column. The mean incidence of side effects is based only on data clearly reported in the literature.

nesias). The routine therapeutic strategy that we implement in our departments is first to subject a patient to single intermittent injections of apomorphine, attempting to anticipate the occurrence of off periods. Only when a patient would require >7–8 injections per day is the infusion pump considered. In some cases, patients can start with single injections and, either because of the poor results obtained with this technique or a progression of the underlying disease, are later infused with a pump.

Subcutaneous apomorphine has proven useful also in the management of some parkinsonian disabilities appearing during off periods. Improvement was reported for distressing belching and aerophagy (39), obstructive defecation (anismus; 40,41), functional bladder outlet obstruction (42), painful dystonic movements, and off period visual hallucinations (26).

The availability of a potent antiparkinsonian drug that can be administered parenterally may also be temporarily useful in some specific situations. For example, apomorphine has been recently used to replace levodopa in patients to whom oral therapy could not be administered (e.g., after a major surgical intervention) (43).

Other Routes

Given the poor compliance of some patients to parenteral drug administration, other routes of application for apomorphine have been exploited (Table 3). It has been shown that apomorphine can easily penetrate mucous membranes (44); therefore, its efficacy after sublingual, intranasal, and rectal routes of administration has been investigated. The sublingual route has the advantage of a longer motor response (mean, 73 min) than the subcutaneous route, but it also has a much longer latency of action (mean, 43 min). By this route, it is necessary to use a 10-fold higher dose to elicit a clinical response comparable to that seen after subcutaneous administration (36,45).

A pilot study on chronic sublingual apomorphine in PD was performed in seven patients, who were treated with doses ranging from 9 to 30 mg t.i.d. without changes in the remaining medications (46). Self-rated daily records showed a mean reduction of off hours by 56% after a treatment lasting an average 4 months. The main adverse reaction was the occurrence of stomatitis, with ulcerations of buccal mucosae and a loss of taste observed in four patients. The severity of this

TABLE 3. *Efficacy, latency, and duration of apomorphine administered by different routes*[a]

Route	Efficacy	Mean latency	Mean duration	Reference
Subcutaneous	100%	7 min	60 min	26
Intravenous	100%			8
Nasal	50%	9 min	44 min	47
Sublingual	10%	43 min	73 min	45
Rectal	1.5%	32 min	195 min	50
Oral	1%			16

[a] The percent efficacy values have been computed, based on the available evidence, as a function of the subcutaneous route.

complication forced discontinuation of sublingual apomorphine; the patients recovered from stomatitis approximately 2 weeks after withdrawal. Because the pathogenetic mechanism of local complications of apomorphine (including skin nodules occurring after a subcutaneous administration) remains unknown, further clinical studies should be carried out using more efficient and better tolerated sublingual formulations having faster dissolution time and, consequently, shorter latency of action.

Intranasal administration exhibits latency and duration of action similar to those seen after the subcutaneous route (47,48). The mean dose of intranasal apomorphine required for a good motor response is close to that used for a subcutaneous injection, ranging between once and twice the value. The chronic use of intranasal apomorphine was subject to a preliminary evaluation in seven patients, six of whom successfully received apomorphine for 9 months, at doses ranging from 1 to 5 mg per application (49). The remaining patient, who used high doses (10 mg), soon developed a severe nasal vestibulitis; therefore, he discontinued intranasal apomorphine after 4 weeks of treatment. A mild vestibulitis also appeared in three other patients after several weeks of intranasal treatment; however, it was not necessary to withdraw the treatment in these cases. These preliminary results seem to support a wider use of intranasal apomorphine spray. Nevertheless, because a significant number of patients develop mucosal irritation, a preliminary otorhinolaryngologic assessment followed by regular controls is advisable.

Apomorphine administration by means of rectal suppositories has also been tried. In a pilot study, 11 patients who already had responded well to subcutaneous apomorphine were given a single test with a suppository containing 200 mg of the drug. Five patients showed a therapeutic effect similar to that seen after subcutaneous administration. In three patients, there was a partial motor response for a short period; in the remaining three, no motor response was detected. In the five cases who responded favorably, the mean latency to motor response was 32 min, and the mean duration of response was 195 min (50). Based on these data, it was suggested that such a long duration of motor benefit after rectal administration might prove useful in patients with significant nocturnal disabilities, as an alternative or an adjunct to sustained-release levodopa preparations.

Diagnostic Use

The clinical diagnosis of PD remains troublesome. In a recent retrospective clinical pathological study, it was found that only 76 of 100 patients who received a clinical diagnosis of PD later satisfied neuropathologic criteria for PD (51). A definite therapeutic response to levodopa is one of the main features required for the diagnosis of PD; a lack of response is believed to be associated with a parkinsonian picture different from PD (52). Only anecdotal cases of histologically proven PD have been reported not to have responded to an adequate trial with levodopa (53); on the other hand, there is increasing evidence that some clinical response to levodopa occurs in parkinsonian syndromes different from PD (e.g., in multiple system atrophy; 54,55).

The objective quantitative measurement of dopaminergic responsiveness helps

to understand whether or not a parkinsonian syndrome responds to dopaminergic therapy. It has been proposed that an acute challenge with dopaminergic agents predicts the response to chronic levodopa, thus improving the accuracy of diagnosis of parkinsonism (56). The rationale of such a test is comparable to the acute challenge to edrophonium, as it is widely used for the diagnosis of myasthenia gravis. The administration of a single oral dose of levodopa was initially proposed as the most logical test; however, because of its pharmacological properties, levodopa has some drawbacks. First, it cannot be used to plot a dose–response curve on a single day. Moreover, its enteric absorption is not granted, and so the accuracy of a clinical evaluation is in question. Based on these considerations, it has been suggested that a dopaminergic agonist given parenterally could provide a better test of dopaminergic responsiveness (57). Apomorphine appears to be the best candidate drug for such a test because of its rapid action, reliability, and safety. The short plasmatic half-life of apomorphine allows for several challenges during a single morning (8), which makes it easy to obtain a dose–response curve.

Apomorphine acute challenge has rapidly gained popularity, and it is now widely employed to assess either previously untreated patients or patients whose response to oral levodopa is unclear. In our departments, the apomorphine challenge is performed in the following way. Domperidone (20 mg t.i.d.) is administered starting 48 h before the test. The test is performed in defined off conditions (i.e., 12 h after withdrawal of antiparkinsonian medications; 58). Apomorphine is given subcutaneously in increasing doses at 60-min intervals. The starting dose is 1.5 mg; it is first increased to 3 mg and then, by 1- or 1.5-mg steps, to 6–8 mg, until either a significant clinical response is recorded or dose-limiting side effects are encountered. Most patients show a clinical response with doses as low as 3 mg; a limited number of patients respond to only very high doses (59). The motor response is assessed by measuring alternate unilateral hand tapping for 30 sec, the walking time (usually on 12 m) and by scoring part III of the *Unified PD Rating Scale* (60). We believe that a response to acute apomorphine challenge is significant when at least two of these items are improved by 20%.

The response to acute apomorphine has been shown to predict the effect of chronic therapy with levodopa in >90% of patients with advanced disease (59) and in 67–85% of patients at their first diagnosis (61,62). Such a discrepancy between the predictive effect in different disease stages may be the result of a variety of causes: (*a*) Mild parkinsonian features may render it difficult to evaluate an improvement by using the standard disability scale or simple motor tests; (*b*) Patients naive to dopaminergic medication often experience autonomic side effects, which may interfere with their motor performance; or (*c*) A placebo effect may be more commonly encountered at early stages of the disease. Because the acute test may not detect a proportion of patients with untreated early parkinsonism, who may nevertheless experience some benefit from a chronic levodopa treatment, a negative response does not imply the elimination of a chronic schedule of oral levodopa.

Similar to edrophonium in myasthenia gravis, the acute apomorphine challenge may also be used to test the clinical benefit in patients treated chronically. In some forms of tremor, in which the response to dopaminergic treatment is unclear, an

apomorphine challenge may be particularly helpful to clarify the diagnosis. Indeed, postural and action tremor are not rare in PD, and sometimes they are indistinguishable from essential tremor. A positive response to apomorphine may rule out tremors other than parkinsonian tremor (63).

Apomorphine has also been widely used to conduct clinical pharmacological studies in PD (64). In contrast to levodopa, which is a neurotransmitter precursor, apomorphine is a direct-acting dopamine agonist. It is lipophilic and quickly equilibrates between plasma and central nervous system compartments. Thus it is well suited for clinical studies on the pharmacodynamics of central dopamine receptors. Two major lines of research have been developed so far. First, the occurrence of tachyphylaxis for dopaminergic drugs, after a few repeated doses, has been the object of a dispute. Some investigators have measured a decline in the response to closely spaced bolus injections of apomorphine (65); on the contrary, others have failed to find any response variation (66). One possible explanation for the conflicting results is that intervals between two consecutive doses varied between these two studies. Indeed, it seems that the duration of response after an acute dose becomes shorter when the interdose interval is 2 h but remains equal if the dose interval is 4 h (67). A second line of research addressed the role of pharmacodynamic variables in the pathophysiology of motor fluctuations that occur in advanced PD. We recently attempted to clarify the role played by presynaptic events, as compared to postsynaptic receptor changes, by measuring the response after an acute challenge with apomorphine in different groups of parkinsonian patients. The motor response after apomorphine administration was longer in previously untreated patients than in levodopa-treated patients with longer disease duration. This indicates that some factors (e.g., central pharmacodynamic alterations) other than a lack of capacity to store dopamine play a role in the pathophysiology of motor fluctuations (68).

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is a severe and often lethal complication induced by neuroleptics or by a sudden reduction of levodopa dosage (69). Its pathophysiology probably depends on a dysregulation of the incerto-hypothalamic dopaminergic neurons, caused either by the action of antidopaminergic drugs or by a sudden withdrawal of dopaminergic drugs (70). The ideal treatment has not been found. Current therapy is based on the available oral dopaminergic drugs, which are usually associated with peripheral muscle relaxants (e.g., dantrolene).

Based on a few published cases of patients affected by NMS, who were successfully treated with lisuride infusions (71), apomorphine was recently proposed as a possible therapy for this rare condition. Only two cases have been reported (72,73). In the first patient, subcutaneous apomorphine was given continuously at a rate of 1 mg/h, in the second patient 2 mg were injected every 3 h. In both cases, an excellent clinical response was observed, with a rapid and complete remission of hyperthermia and rigidity. These results indicate that apomorphine is probably the most rational drug currently available for the treatment of NMS.

HUNTINGTON'S DISEASE

The clinical efficacy of apomorphine on chorea associated with rheumatic fever was first described in the nineteenth century by Pierce (3) and by Weil (4). More recently it was found that, in contrast to levodopa (74), several dopaminomimetics, including apomorphine, can ameliorate Huntington's disease (HD) chorea when they are administered at low doses. This symptomatic treatment has been thought to selectively stimulate presynaptic D_2 dopamine receptors, thus inhibiting neuronal firing in the neostriatum (75). This is in keeping with the accepted explanation for a sharp difference in the behavioral effects induced by apomorphine, which are possibly due to the stimulation of pre- and postsynaptic dopamine receptors, respectively. Indeed, in experimental animals, apomorphine influences behavioral responses in a biphasic manner: at low doses, it produces sedation (which is thought to be mediated by presynaptic receptors): at higher doses, it causes hypermotility and sterotypy (probably due to a stimulation of the postsynaptic receptors) (76).

The putative antichoreatic action of apomorphine has gained growing recognition, partly based on the availability of domperidone, which prevents its peripheral side effects (77). Central side effects consist mainly of sedation because psychosis, which occurs in HD patients treated with other dopaminergic drugs, has never been reported. By contrast, the amelioration of chorea is observed at the same doses (0.05 mg/kg) therapeutically used for PD (78,79). If these observations were confirmed by larger placebo-controlled trials, it would be difficult to explain the efficacy of apomorphine in HD as due to its action on presynaptic dopamine receptors. Alternatively, such clinical properties of apomorphine could be related to its effect on other neurotransmitter receptors (e.g., neuropeptides); indeed, it has been reported that a pretreatment with the opiate antagonist naloxone can partially counteract some central side effects of apomorphine, such as sedation, yawning, and respiratory depression (80). This assertion requires further confirmation, however. A point that deserves further analysis is also whether there is any correlation between a positive acute response to apomorphine in chorea and the subsequent response to a chronic low-dose therapy with oral agonists.

DYSTONIA

Some forms of dystonia, which account for up to 12% of all childhood and juvenile idiopathic forms, can respond to dopaminergic drugs (81). The detection and treatment of these patients is an important task for the clinician, because in these cases of dystonia, an appropriate pharmacological treatment may significantly change the clinical outcome. Therefore, a trial with dopaminergic drugs is usually performed in dystonic patients at the time of diagnosis.

The first report of a reduction of involuntary movements in idiopathic and secondary dystonia by apomorphine was already published in the 1970s (82). After the diffusion of apomorphine as a test drug for dopaminergic responsiveness in PD, it was also proposed as a tool for predicting the response to levodopa in

selected cases of idiopathic dystonia (83). The results of a placebo-controlled trial of subcutaneous apomorphine in seven cases of segmental and generalized dystonia showed a significant clinical response in five, at doses similar to those used in PD. All patients who reacted positively to apomorphine experienced an improvement with a chronic dopaminergic therapy (levodopa plus lisuride or apomorphine); they were therefore classified as having levodopa-responsive dystonia. The response to chronic levodopa was more remarkable in patients who responded to low doses of apomorphine. The two patients who failed to respond to the acute challenge showed no benefit from chronic treatment with dopaminergic drugs. The usefulness of apomorphine as a diagnostic tool for levodopa-responsive dystonia has been recently confirmed (84): it has also been reported that it can be used as an effective treatment in selected cases. Still, larger and better-designed trials are warranted to better define the diagnostic role and the possible therapeutic efficacy of apomorphine in dystonia.

CONCLUSIONS

Despite the stated drawbacks, apomorphine represents a major therapeutic breakthrough in a limited group of severely affected PD patients with marked motor fluctuations. This treatment significantly improves the quality of life in patients who have experienced many other therapeutic stratagems. For this reason, it seems reasonable to propose a carefully supervised trial of apomorphine in the hospital before considering a patient pharmacologically intractable. The application of apomorphine on different mucosae (lingual, nasal, rectal) is an effective approach, which is often associated with a dose-dependent, reversible, local irritation. This can limit, to an extent that is still unknown, the use of such alternative routes of administration. Thus larger studies with better tolerated and more efficient preparations (e.g., sublingual tablets with faster dissolution time) should be carried out. It may also be hypothesized that a prolongation of the short plasmatic half-life of apomorphine could be achieved by manipulating its biochemical structure: this is still one of the major limitations to a larger use of apomorphine as an anti-parkinsonian drug in the early disease stage.

We propose that parenteral apomorphine be considered the first-choice treatment for parkinsonian patients who require a sudden withdrawal of oral levodopa (e.g., after gastrointestinal surgery). This would not only allow for a substitution therapy but also would prevent the occurrence of an NMS. In addition, apomorphine could be considered the first-choice treatment for NMS induced by neuroleptics. Because these conditions are potentially life threatening, an infusion therapy with this potent dopamine agonist is certainly warranted.

As a diagnostic tool, acute apomorphine challenge represents a rapid, safe, and quite reliable index of dopaminergic responsiveness. This test is helpful in selecting patients for trials with a new antiparkinsonian drug or before addressing them to surgical treatment (e.g., stereotactic brain lesions, deep brain stimulation, intracerebral grafts). Thus apomorphine challenge allows idiopathic PD cases to be more accurately identified, with a consequent improvement in the outcome of any procedure based on a reliable clinical diagnosis.

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